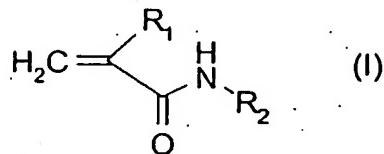


CLAIMS

1. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,
5 - an acryloyl distamycin derivative of formula (I):



wherein:

R₁ is a bromine or chlorine atom;

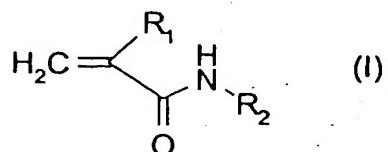
R₂ is a distamycin or distamycin-like framework; or a pharmaceutically acceptable salt
10 thereof; and

- a protein kinase inhibitor.

2. A pharmaceutical composition according to claim 1 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, PKI 166,
15 EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosine, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11248, Flavopiridol, and CI-202.

- 20 3. A pharmaceutical composition according to claim 2 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774 and SU 5416.

4. A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative of formula (I)

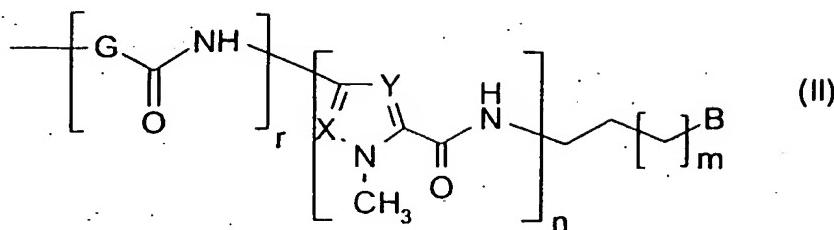


25

wherein:

R₁ is a bromine or chlorine atom;

R₂ is a group of formula (II)



wherein

m is an integer from 0 to 2;

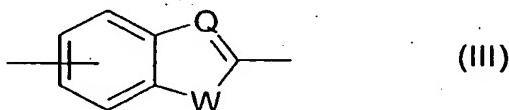
5 n is an integer from 2 to 5;

r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

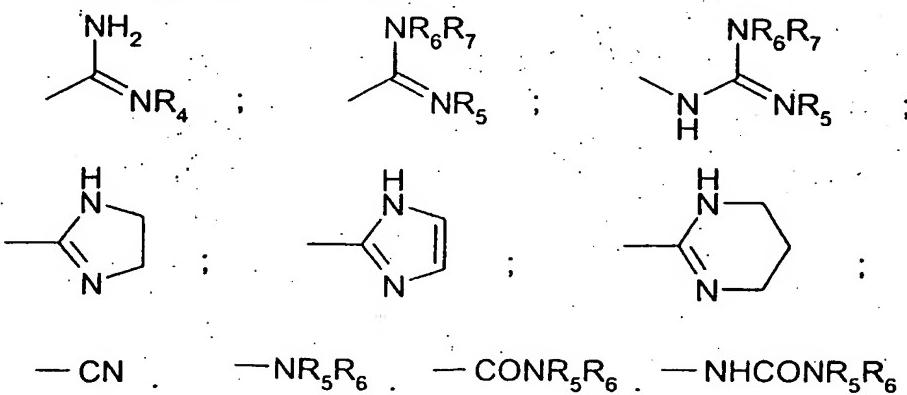
G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1

10 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR₃ wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of

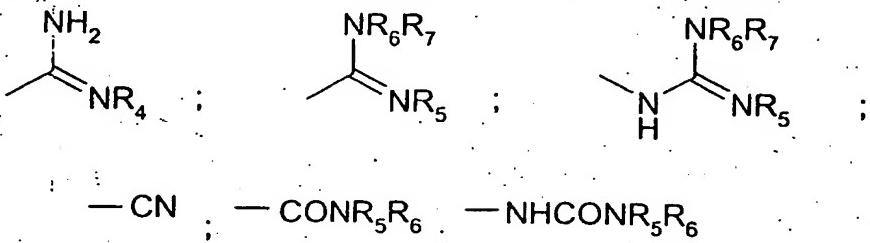


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wherein R₄ is cyano, amino, hydroxy or C₁-C₄ alkoxy; R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

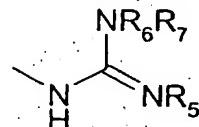
5. A pharmaceutical composition according to claim 4 comprising an acryloyl

distamycin derivative of formula (I) wherein R₁ and R₂ are as defined in claim 4, r is 0, m is 0 or 1, n is 4, X and Y are both CH groups and B is selected from:



wherein R₄ is cyano or hydroxy and R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

6. A pharmaceutical composition according to claim 5 comprising an acryloyl distamycin derivative of formula (I) wherein R₁ is bromine, R₂ is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula



10

wherein R₅, R₆ and R₇ are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt.

7. A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative, optionally in the form of a pharmaceutically acceptable salt, selected from the group consisting of:

1. N-[5-[[5-[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin);
2. N-(5-{{(5-{{(5-{{(2-{{(amino(imino)methyl)amino}propyl)amino}carbonyl}}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;
- 25 3. N-(5-{{(5-{{(5-{{(3-amino-3-iminopropyl)amino}carbonyl}}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl)-1-methyl-1H-pyrrol-3-yl]amino]carbonyl)-1-methyl-1H-

pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

4. N-(5-{{(5-{{(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-

yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-

5 pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-imidazole-2-carboxamide hydrochloride;

5. N-(5-{{(5-{{(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-

yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-

pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide

10 hydrochloride;

6. N-(5-{{(5-{{(3-amino-3-oxopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-

yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-

pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide;

7. N-(5-{{(5-{{(2-{{[amino(imino)methyl]amino}ethyl)amino]carbonyl}-1-

methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-

yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-

methyl-1H-pyrrole-2-carboxamide hydrochloride;

8. N-(5-{{(5-{{(3-{{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-

1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-

20 bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

9. N-(5-{{(5-{{(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-

yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-

methyl-1H-pyrrole-2-carboxamide hydrochloride; and

10. N-{5-{{5-{{5-[(3-[(aminocarbonyl)amino]propyl)amino]carbonyl}-1-methyl-

1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl}amino]carbonyl}-1-

methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-

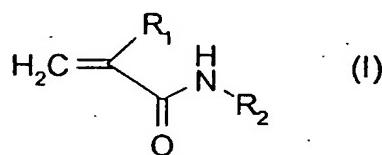
carboxamide.

8. A pharmaceutical composition comprising a pharmaceutically acceptable

30 carrier or excipient and, as active ingredient,

- N-[5-[[[5-[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin); and
- 5 - a protein kinase inhibitor selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

9. Products comprising an acryloyl distamycin derivative of formula (I):



10 wherein:

R_1 is a bromine or chlorine atom;

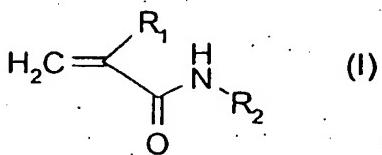
R_2 is a distamycin or distamycin-like framework; or a pharmaceutically acceptable salt thereof; and a protein kinase inhibitor, as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

15

10. Products according to claim 9 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, PKI 166, EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosine, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11248, Flavopiridol, and CI-20.

11. Products according to claim 10 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774 and SU 5416.

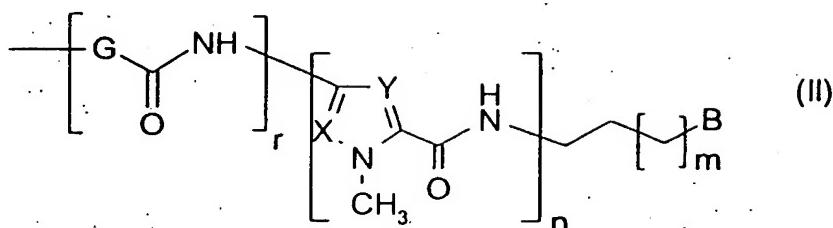
25 12. Products according to claim 9 comprising an acryloyl distamycin derivative of formula (I)



wherein:

R₁ is a bromine or chlorine atom;

R₂ is a group of formula (II)



5 wherein

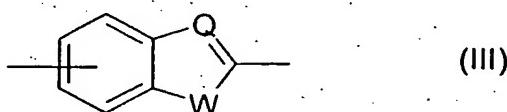
m is an integer from 0 to 2;

n is an integer from 2 to 5;

r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

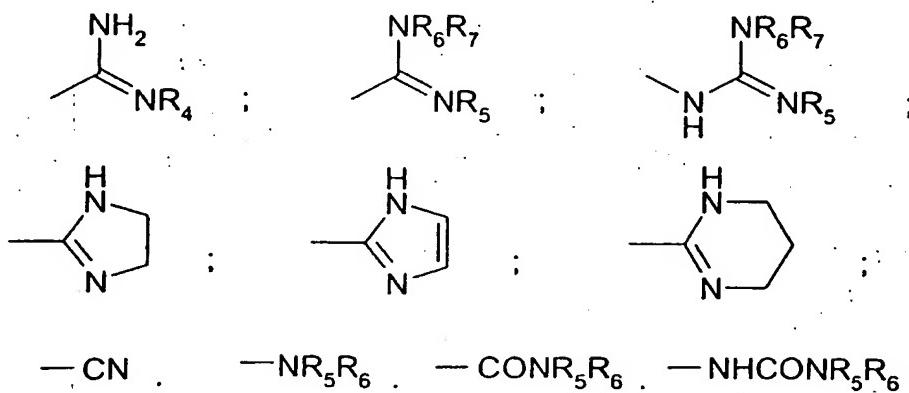
10 G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a

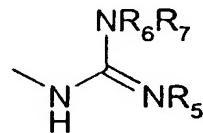
15 group NR₃ wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of



wherein R₄ is cyano, amino, hydroxy or C₁-C₄ alkoxy; R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

13. Products according to claim 9 comprising an acryloyl distamycin derivative of formula (I) wherein R₁ is bromine, R₂ is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula



5 wherein R₅, R₆ and R₇ are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt.

14. Products according to claim 9 wherein the acryloyl distamycin derivative is selected from the group as defined in claim 7.

10

15. Products comprising the acryloyl distamycin derivative N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and a protein kinase inhibitor selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416; as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

15

16. Use of an acryloyl distamycin derivative of formula (I), as defined in claim 1, in the preparation of a medicament to be used in combination therapy with a protein kinase inhibitor, in the treatment of tumors.

20

17. Use according to claim 16 wherein the medicament further comprises the said protein kinase inhibitor.

25

18. Use according to claims 16 or 17 wherein the protein kinase inhibitor is as defined in claim 2.

19. Use according to claims 16 or 17 wherein the acryloyl distamycin derivative is selected from the group as defined in claim 7.

20. Use of the acryloyl distamycin derivative N-[5-[[[5-[[[2-
5 [(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-
yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-
propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-
carboxamide hydrochloride (Brostallicin), in the preparation of a medicament to be
used in combination therapy with a protein kinase inhibitor selected from the group
10 consisting of STI571, ZD-1839, OSI-774, and SU 5416, in the treatment of tumors.

21. Use according to any one of claims from 16 to 20 wherein the tumor is selected from breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors.

15

22. Use of an acryloyl distamycin derivative of formula (I), as defined in claim 1, in the preparation of a medicament to be used in combination therapy with a protein kinase inhibitor, in the prevention or treatment of metastasis or in the treatment of tumors by inhibition of angiogenesis.

20

23. Use according to claim 22 wherein the medicament further comprises the said protein kinase inhibitor.

24. A method of treating a mammal, including humans, suffering from a neoplastic disease state, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

25. A method according to claim 24 wherein the acryloyl distamycin derivative is
30 N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-
3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-

propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

- 5 26. A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent, in a mammal in need thereof including humans, the method comprising administering to said mammal a combined preparation comprising a protein kinase inhibitor and an acryloyl distamycin derivative of formula (I), as defined in claim 1, in amounts effective to produce a synergistic antineoplastic effect.

10

27. A method according to claim 26 wherein the acryloyl distamycin derivative is N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

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